Less Pathological Axillary Involvement is Observed in Breast Cancer Patients with Autoimmune Thyroid Disease

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Research

Keywords: Thyroid autoimmune, breast cancer, prognostic factors

Posted Date: March 11th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-16785/v1

Abstract

Background: Autoimmune thyroid disease is more frequently observed in breast cancer patients. There are not enough studies showing the prognostic significance of this association in terms of breast cancer. The aim of this study was to determine the breast cancer molecular subgroup frequency and to examine the relationship between autoimmune thyroid disease and the breast cancer in terms of prognosis and predictive factors.

Methods: One hundred and one patients have been included to study. They have been divided into subgroups according to molecular classification. The patients with high serum anti-thyroid peroxidase levels were considered positive for autoimmune thyroid disease. Prognostic and predictive parameters [tumor stage, tumor size, axillary lymph node involvement, histologic grade, lymphovascular , perineural invasion, hormone receptor status, HER2 (Human Epidermal Growth Receptor 2) over expression] were compared between breast cancer patients with autoimmune thyroid disease and those patients without autoimmune thyroid disease.

Results: The prevalence of thyroid autoimmunity was 23.8% (n = 24) in breast cancer patients. The axillary lymph node involvement in autoimmune thyroid disease positive breast cancer patients was lower than autoimmune thyroid disease negative patients (37.5% versus 61% respectively, p = 0.043). There were no significant differences between the two groups in terms of other prognostic parameters. More importantly, there was a significantly negative correlation between anti thyroid peroxidase levels and axillary lymph node involvement in patients (r= -0.245, p=0.014).

Conclusion: Positive axillary lymph nodes, have been found to be lower in breast cancer patients accompanied by autoimmune thyroid disease. This result supports the view that thyroid autoimmunity is a positive prognostic factor in terms of breast cancer. The mechanism through which it is effective should be examined in new studies. Trial registration: A written approval was granted by the Kirikkale University, Faculty of Medicine, Clinical Research Ethics Committee through the 01/09 Numbered and 19.01.2016 Dated Decision in order to conduct this study.

Keywords: Thyroid autoimmune, breast cancer, prognostic factors

Introduction

Breast cancer is the most common malignant tumor found in women all over the world and following lung cancer, it is the second most common cause of cancer related deaths in women[1]. The natural course of breast cancer varies among patients. In some patients with the same tumor diameter, tumor recurrence occurs in a very short period of time while others remain healthy. For this reason, prognostic factors such as tumor size, axillary lymph node involvement, histologic tumor type, histologic grade, hormone receptors (estrogen and progesterone receptors (ER, PR)], tumor proliferation rate, molecular factors such as enzymes, HER2 (Human Epidermal Growth Receptor 2) and onco-suppressor genes

[Breast Cancer Susceptibility (BRCA), p53, cathepsin-D] are used in order to identify clinical and biological behavioral differences [1].

The most powerful prognostic factor in breast cancer is axillary lymph node involvement.[2] Nowadays, in addition to axillary lymph node involvement, other important factors such as steroid hormone receptor status was efficient in prognosis and treatment, HER2, are used for this purpose. Additionally, the effects on the prognosis of the differences in molecular definitions have become the new targets of the researchers. [3] As a result of the developments in quantitative revert transcriptase polymerase chain reaction and microarray technology, the molecular gene expression profiles of breast cancers have been exposed and breast cancer has been classified according to this heterogeneous pattern. According to the new molecular classification of breast carcinoma, carcinomas carrying the ER are located in the group with the good course. It also benefits to a great degree from the Anti-estrogen treatment [4]. The worst prognostic group is HER2 (+) and the triple (HER2, ER, PR) negative breast carcinomas.

In some studies, the prevalence of autoimmune thyroid disease (AITD) was found to be higher in patients with breast cancer [5, 6]. Both breast cancer and thyroid diseases are women suggest that a number of common factors may be effective in the etiology of these two diseases. Genetic predisposition to the Hashimoto's thyroiditis (X chromosome), sex steroids, decreased T and B cell function with a significant increase in CD24 + and CD25 + T cells during pregnancy, immune hyperactivity caused by stress induced hypercortisolemi or high corticotropin releasing hormone levels, viral infection, excessive iodine uptake, radiation exposure after the Chernobyl nuclear accident and fetal microchimerism are known as possible risk factors for Hashimoto thyroiditis. There are not enough studies showing the prognostic significance of autoimmune thyroid disease in patients with breast cancer in the medical literature.

The aim of our study was to determine the breast cancer molecular subgroup frequency and to examine the relationship between AITD and the breast cancer in terms of prognosis and predictive factors.

Material And Methods

One hundred and one women who were followed up at Kirikkale University Medical Faculty Research and Practice Hospital, Medical Oncology outpatient clinics with a diagnosis of breast cancer were included in our study [mean age 57.93 ± 13.44 (range 33–89) years]. Patients diagnosed with other types of cancer outside of breast cancer, those with an autoimmune disease other than autoimmune thyroid disease, immunodeficiency, those with thyroid hormone replacement therapy were excluded from the study. The postoperative pathology reports and medical record in study population were reviewed retrospectively.

Autoimmune thyroid disease was diagnosed when the level of anti-TPO (thyroid peroxidase) was above 34 IU / mL and thyroid parenchyma image on the thyroid ultrasound was heterogeneous.

A retrospective review was conducted of the post-operation pathology reports of the patients concerning the phase of the American Joint Committee on Cancer (AJCC) phase classification, [7] diameter of the

tumor, the histologic grade of the tumor according to the Modified Scarff-Bloom-Richardson grading system, lymphovascular and neural invasion status, hormone (estrogen and progesterone) receptor status, HER2 expression and the axillary lymph node involvement. The axillary lymph node involvement was considered positive in all axillary lymph nodes in the same side of the tumor with a metastasis greater than 0.2 mm. Invasion of the tumor of the surrounding lymphatic and vascular structures was considered as a lymphovascular invasion. As for the HER2 evaluation, while tumors detected with 3 + through immunohistochemistry or those detected with 2 + and subject to a fluorescence in situ hybridization (FISH) test in which amplification was observed were accepted as HER2 positive while other tumors were accepted as negative. Tumors with a molecular subtype classification of estrogen and/or progesterone receptor positive as well as those with negative HER2 tumors were grouped as "Luminal A", while those with an estrogen and/or progesterone receptor positive as well as positive HER2 tumors were grouped as "Luminal B"; in addition to tumors with an estrogen and/or progesterone receptor negative as well as positive HER2 tumors which were grouped as "HER2 over expression" and those tumors with estrogen and/or progesterone receptors negative as well as negative HER2 tumors which were grouped as "Triple negative". A written approval was granted by the Kirikkale University, Faculty of Medicine, Clinical Research Ethics Committee through the 01/09 Numbered and 19.01.2016 Dated Decision in order to conduct this study.

Free T3 and free T4 were determined by electrochemiluminescence emission technique and TSH levels by electochemiluminescence Immuno Assay (Roche Diagnostics, Meinhaim, Germany).

Statistical analysis:

The data of the study has been recorded with the program Statistical Package for the Social Sciences (SPSS) version 20 (IBM corporation, New York, United States) and statistically analyzed has been carried out. Descriptive statistics are depicted as number, percentage, mean and standard deviation. The chi-square test was implemented to compare qualitative data. The normal distribution suitability of the variables was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov, Shapiro-Wilk tests). Numerical variables determined according to normal distribution, were compared between the two groups using Independent T test. Numerical variables with no normal distribution were compared between the two groups using the Mann Whitney U test. The relationships between variables were evaluated with Spearman’s correlation analysis. In the analysis results, it is considered significant that the value of p was less than 0.05.

Results

While the mean age of breast cancer patients with autoimmune thyroid disease was 58,58 ± 13,94 years, the mean age of breast cancer patients without autoimmune thyroid disease was 57.73 ± 13.37 years. There was no significant difference between the groups in terms of age distribution. Serum thyroid hormones, TSH and anti TPO levels in our study population were demonstrated Table 1. The prevalence of autoimmune thyroid disease in our study was 23.8% (n = 24) in breast cancer. In addition, 79.2% (n =

19) of women with breast cancer diagnosed with AITD were found to be euthyroid, 8.3% (n = 2) subclinical hypothyroid, 8.3% (n = 2) overt hypothyroid and 4.2% (n = 1) subclinical hyperthyroid. 79.2% (n = 61) of women with breast cancer diagnosed without AITD (n = 77) were found to be euthyroid, 10,4% (n = 8) subclinical hypothyroid and 3.9% (n = 3) overt hypothyroid, and 2.6% (n = 2) hyperthyroidism.

Table 1
Serum thyroid hormones, TSH and TPO levels in study pooplation with breast cancer

	Breast Ca with AITD n:24	**Breast Ca without AITD n:77**	**p**
FreeT3 (pg/mL)	2.70 ± 0.52	3.03 ± 0.52	0.009
Free T4 (ng/dL)	1.17 ± 0.19	1.26 ± 0.22	0.08
TSH (µU/mL)	3.47 ± 3.67	2.56 ± 1.96	0.256
AntiTPO (IU/mL)	216.39 ± 167.54	9.96 ± 5.24	0.0001

It has been found that invasive ductal carcinoma in 91.6% (n = 22) of breast cancer patients with AITD, 4,2% (n = 1) invasive lobular carcinoma, 4.2% (n = 1) other subtypes. Invasive ductal carcinoma in 93.5% (n = 72) of breast cancer patients without AITD, invasive lobular carcinoma in 3,9% (n = 3) and other subtypes in 2.6% (n = 2). No significant difference was found in histological subtype distribution among the group with autoimmune thyroid disease and the group without autoimmune thyroid disease. No significant differences were found between the group with autoimmune thyroid disease and the group without autoimmune thyroid disease in terms of tumor size, tumor stage, molecular subgroup distribution, hormone receptor positivity and tumor grade (Table 2). However, axillary lymph node involvement in breast cancer patients without 24 AITD (n = 9) was higher than in breast cancer patients with 77 AITD (n = 47) [(61% vs. 37.5%, respectively (p = 0.043)] (Table 2).

Table 2
Cytopathologic feature of breast cancer in study population

	Breast Ca with AITD n:24	Breast Ca without AITD n:77	p
Tumor size (cm)	2.47 ± 1.17	2.79 ± 1.69	0.585
Stage Stage 1 Stage 2 Stage 3 Stage 4	6 (25.0%) 13 (54.2%) 1 (4.2%) 4 (16.7%)	16 (20.8%) 39 (50.6%) 9 (11.7%) 13 (16.9%)	0.744
Histological subtype: Invasive ductal carcinoma Invazive lobuler carcinoma Other	22 (91.6%) 1 (4.2%) 1 (4.2%)	72 (93.5%) 3 (3.9%) 2 (2.6%)	0.922
Estrogen receptor Positive Negative	18 (75.0%) 6 (25.0%)	60 (77.9%) 17 (22.1%)	0.766
Progesterone receptor Positive Negative	16 (66.7%) 8 (33.3%)	55 (71.4%) 22 (28.6%)	0.656
HER2 overexpiration Positive Negative	9 (37.5%) 15 (62.5%)	36 (46.8) 41 (53.2)	0.426
Grade Grade 1 Grade 2 Grade 3	5 (20.8%) 15 (62.5%) 4 (16.7%)	10 (13.0%) 40 (51.9%) 27 (35.1%)	0.207
Axillary lymph node involvement Positive Negative	9 (37.5%) 15 (62.5%)	47 (61.0%) 30 (39.0%)	0.043
Neural invasion Positive Negative	3 (12.5%) 21 (87.5%)	8 (10.4%) 69 (89.6%)	0.720
Peritumoral lymphovascular invasion Positive Negative	5 (20.8%) 19 (79,2%)	13 (16.9%) 64 (83.1%)	0.761

On the other hand, there was no significant difference in terms of neural invasion and peritumoral lymphovascular invasion among the groups (Table 2). In 54.2% (n = 13) of the breast cancer patients with autoimmune thyroid disease were Luminal A, 20.8% (n = 5) Luminal B, 16.7% (n = 4) HER2 over expression. In 8.3% (n = 2) triple negative breast cancers while 49.4% (n = 38) of breast cancer patients without autoimmune thyroid disease in Luminal A, 31.2% (n = 24) Luminal B, HER2 overexpression in

15.6% (n = 12) and 3.9% (n = 3) triple negative breast cancer. There was no significant difference between the groups in terms of autoimmune thyroid disease and molecular subgroup distribution (p = 0.681).

There was a positive correlation between serum TSH levels and anti- TPO levels (r = 0.240, p = 0.016). More importantly, there was a significantly negative correlation between anti TPO levels and axillary lymph node involvement in patients with breast carcinoma (r= -0.245, p = 0.014).

Discussion

Determine of prognostic and predictive factors in breast cancer are very important in the high-risk group, because the differences of the clinical and biological behavioral of breast cancer vary among patients. According to our finding the presence of thyroid autoimmunity in our patients with breast cancer may show a positive prognosis due to low axillary lymph node involvement which is an important prognostic parameter independent of other clinical outcome. More importantly, we found a significantly negative correlation between anti TPO levels and axillary lymph node involvement in patients with breast carcinoma. According to the limited number of studies in medical literature, axillary lymph node involvement rate in patients with breast cancer accompanied by autoimmunity was lower than the ones without autoimmunity (22% vs.46%, p = 0,007)[14]. On the other hand, Cengiz et al. [8] found that the number of lymph nodes involved in breast cancer patients with thyroid disease was greater than that of breast cancer patients without thyroid disease (p = 0,005). Unlike previously reported studies, we firstly demonstrated that there was a significantly negative correlation between anti TPO levels and axillary lymph node involvement in patients with breast carcinoma. It seems that antithyroid peroxidase antibody positivity may be associated with a lower incidence of axillary metastases in newly diognosis breast cancer.

Although the pathogenesis is not fully understood, it is suggested that combined iodine-selenium deficiency may facilitate the development of breast cancer. Both thyroid and breast tissue shows similar properties in terms of iodine and selenium metabolism. Both tissues contain the sodium-iodide symporter carrier. On the other hand, excessive iodine uptake and selenium deficiency may contribute to autoimmune thyroid disease. It was reported that increase of selenium level in the diet to cause a decrease in anti-TPO levels. The effect of thyroid autoimmunity and dysfunction is contradictory in the course of patients with breast cancer. Various studies showed that hypothyroidism was associated with the risk of breast cancer development[5,6]. On the other hand, other studies showed that primary hypothyroidism decrease breast cancer incidence[9,10]. Various authors believe that hypothyroidism, autoimmune thyroiditis, and positive serum anti-TPO levels have good outcomes in breast cancer cases. On the other hand, in a recent meta-analysis, it was found that the risk of developing breast cancer in people with AITD was high and an interesting reciprocal link.(odds ratio:2,92) [11]. According to another theory, natural and inducible CD4+, CD25+, Forkhead box P3 (FOXP3)+, regulatory T cells (Tregs) and their co-regulators T helper 17 cells which inhibit autoreactive immune clones and regulate TH1/TH2 shift in autoimmun disease via IL-17A, IL-17F, IL-21, IL-22 and IL- 26, may play important roles in maintaining

immune self-tolerance and the inhibition of both inflammation and cancer.[12] We consider that the advanced immunologic study may clarify possible understanding mechanisms for effect of AITD in prognosis of breast carcinoma.

Interestingly, Sympth et al. [13] previously detected a TPO protein in neoplastic breast epithelium by immunofluorescence. According to their opinion, there was a shared antigen that indicate target for humoral or cell-mediated immune activity associated with both of breast cancer and thyroid (etc.the sodium/iodide symporter, cross-reacting epitopes in TPO or TPO itself and lactoperoxidase). This may explain the high frequency and protective role of TPOAb in breast cancer.

Mucinous, papillary, medullary, adenoid cystic, tubular breast carcinomas have better prognosis compared with the invasive ductal carcinoma and invasive lobular carcinoma. However, micropapillary and metaplastic carcinoma have worse prognosis. In our study, there was no difference in terms of histological subtypes of breast cancer in patients with and without autoimmune thyroid disease.

It was well known that tumor size correlated with lymph node involvement in breast cancer, but their prognostic importance was independent of each other. In a cohort study involving 24,740 patients with breast cancer, 5-year survival rates were found to be 91%, 80% and 63% when the tumor size is 2 cm, 2–5 cm, and > 5 cm, respectively. In our study, although the mean tumor diameter of breast cancer patients with autoimmune thyroid disease was smaller than the mean tumor diameter of breast cancer patients without autoimmune thyroid disease (2.79 ± 1.17 cm versus 2.79 ± 1.69 cm, respectively), no statistically significant difference was found in terms of tumor size between groups (p = 0.585). Similarly, Özmen et al. reported that there was no significant difference in terms of tumor size in breast cancer patients with and without autoimmune thyroid disease (2.49 ± 1.45 cm vs 2.46 ± 1.38 cm)(p = 0.89) [14]. Unlike our results, Cengiz et al.[8] have shown that tumor size was greater in breast cancer patients with thyroid disease (p = 0,023).

In studies in the medical literature have been shown that estrogen receptor-positive cases live longer than estrogen receptor negative cases. In estrogen / progesterone receptor positive breast cancers within the first 5 years, disease-free survival is higher than receptor-negative breast cancers and recurrence rate is lower. Often the estrogen receptor carries a strong predictive value for disease-free survival; whereas progesterone receptors are associated with overall survival, as hormone therapy is more likely to respond in the event of disease recurrence. In our study, the proportion of patients with estrogen receptor-positive patients was found to be 77.2% (n = 78) and the proportion of patients with progesterone receptor-positive patients was found to be 70.3% (n = 71), which was slightly higher than the general literature. In a study conducted by Freitas et al. [15] there was no significant difference in terms of hormone receptor status (ER and PR) between breast cancer patients with autoimmune thyroid disease and breast cancer patients without autoimmune thyroid disease. (p = 0,052). When our study examined the hormone receptor status of breast cancer patients with autoimmune thyroid disease and without autoimmune thyroid disease, there was no significant difference in terms of hormone receptor positivity between the groups.

HER2 overexpression is a poor prognostic factor in patients with positive or negative lymph node involvement [16]. Previous studies indicating that HER2 positivity shows reduced survival even when axillary lymph node involvement is positive. In a study conducted by Freitas et al. [15], there was no significant difference in terms of HER2 overexpression between breast cancer patients with autoimmune thyroid disease and breast cancer patients without autoimmune thyroid disease. In our study, there was also no significant difference between study groups in terms of HER2 overexpression (p = 0.426).

The presence of peritumoral lymphovascular invasion is a poor prognostic indicator, especially in high-grade tumors. Özmen et al. [14] reported that peritumoral lymphovascular invasion was 58% in patients without autoimmune thyroid disease, and 43% in patients with breast cancer accompanied by autoimmune thyroid disease (p = 0,116). In our study, peritumoral lymphovascular invasion rate was lower (17.8%), and there was no significant difference in terms of peritumoral lymphovascular invasion between the groups. Normal and neoplastic breast epithelial cells express thyroid hormone receptors and thyroid hormones show an in vitro tumor-promoting effect .In particular, they induce estrogen-like differentiation and lobular growth of breast tissue[17].

In the conclusion, it has been observed that in cases of breast cancer with autoimmune thyroid disease axillary lymph node involvement is less common than breast cancer with no autoimmune thyroid disease. Thus, autoimmune thyroid disease may be a positive prognostic indicator in breast cancer surveillance. It is recommended that this positive prognostic marker be taken into account in breast cancer surveillance analyzes. For a better understanding of this positive display, prospective studies have to be done.

Abbreviations

Autoimmune thyroid disease (AITD), thyroid peroxidase (TPO), HER2 (Human Epidermal Growth Receptor 2), estrogen receptor (ER), progesterone receptor (PR), Breast Cancer Susceptibility (BRCA), fluorescence in situ hybridization (FISH)

Declarations

Acknowledgements

Not applicable.

Authors' contributions

SY and RC designed and performed the clinical analyses and wrote the manuscript. The authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

The experimental procedures of this study were approved by the Ethics Committee of Kirikkale University, Faculty of Medicine, and an informed consent was received from each participant.

Consent for publication

Written informed consent for publication was obtained from each participant.

Competing interests

The authors declare that they have no competing interests.

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